BRIEF COMMUNICATION

THRESHOLD FOR REPETITIVE ACTIVITY FOR A SLOW STIMULUS RAMP:

A Memory Effect and Its Dependence on Fluctuations

JOHN RINZEL AND STEVEN M. BAER
Mathematical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

ABSTRACT We have obtained new insights into the behavior of a class of excitable systems when a stimulus, or parameter, is slowly tuned through a threshold value. Such systems do not accommodate no matter how slowly a stimulus ramp is applied, and the stimulus value at onset of repetitive activity shows a curious, nonmonotonic dependence on ramp speed. (Jakobsson, E. and R. Guttman. *Biophys. J.* 1980. 31:293–298.) demonstrated this for squid axon and for the Hodgkin-Huxley (HH) model. Furthermore, they showed theoretically that for moderately slow ramps the threshold increases as the ramp speed decreases, but for much slower ramp speeds threshold decreases as the ramp speed decreases. This latter feature was found surprising and it was suggested that the HH model, and squid axon in low calcium, exhibits reverse accommodation. We have found that reverse accommodation reflects the influence of persistent random fluctuations, and is a feature of all such excitable systems. We have derived an analytic condition which yields an approximation for threshold in the case of a slow ramp when the effect of fluctuations are negligible. This condition predicts, and numerical calculations confirm, that the onset of oscillations occurs beyond the critical stimulus value which is predicted by treating the stimulus intensity as a static parameter, i.e., the dynamic aspect of a ramp leads to a delay in the onset. The condition further demonstrates a memory effect, i.e., firing threshold is dependent on the initial state of the system. For very slow ramps then, fluctuations diminish both the delay and memory effects. We characterize the class of excitable systems for which these behaviors are expected, and we illustrate the phenomena for the HH model and for a model of cAMP-receptor dynamics in *Dictyostelium discoideum*.

Excitable systems may spontaneously oscillate if parameter values or stimulus intensities are tuned into appropriate ranges. For a wide class of theoretical models for electrically excitable membranes (1–3), as well as for other types of excitable biological systems (4, 5), the threshold parameter values for oscillatory behavior may be characterized explicitly. At criticality, the system response changes from a damped to a maintained oscillation; here, the decay rate of the damped oscillation passes through zero and this decay rate is determined from a mathematical analysis of linear stability. In order to compare experimental results with this theoretical prediction, one might then ramp the stimulus or parameter sufficiently slowly through criticality to observe the onset of oscillations. This dynamic aspect of the tuning however introduces some additional effects which have significant consequences for the interpretation of threshold. One finds that the onset of oscillations is not observed until the parameter value has passed well beyond the predicted criticality, i.e., there is a delay in the onset (Fig. 1) and an associated memory effect. Moreover, the delayed threshold depends nonmonotonically upon the ramp speed, with decreasing behavior for very slow ramps. This decrease in apparent threshold is surprising to a physiologist who expects that accommodation would lead to the opposite trend. We have obtained new insights into the delay/memory effect and have identified the source of nonmonotonicity with the profound effect of persistent fluctuations as such a system passes through criticality.

The first observations of delayed onset and dependence upon ramp speed were brought to attention in the biophysical literature by Jakobsson and Guttman (7, 8) who reported on experiments with squid axon and numerical calculations with the Hodgkin-Huxley (HH) equations (1). This model shares the essential qualitative feature with a class of excitable/oscillatory systems: repetitive

Steven M. Baer's present address is Dept. of Mathematics, Arizona State University, Tempe, AZ 85287-1804.
Please address all correspondence to Dr. John Rinzel, NIH, NIDDK, MRB, Bldg. 31, Rm. 4B-54, 9000 Rockville Pike, Bethesda, MD 20892

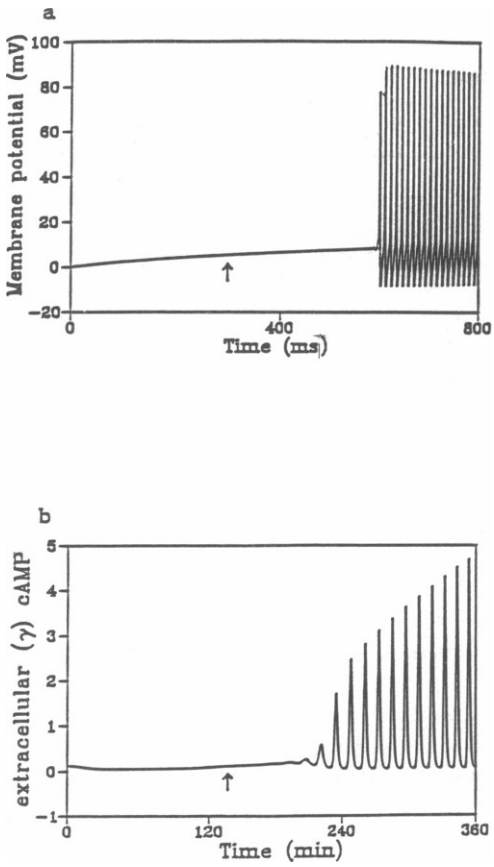

FIGURE 1 Delayed onset of oscillations for slow ramp of stimulus or control parameters in models of two different excitable systems. Vertical arrows correspond to threshold conditions at which maintained oscillations would first occur for steady parameter values. (*A*) Voltage time course for standard Hodgkin-Huxley model (1) of electrical behavior of squid axon under applied current ramp, $I = Rt + I_0$ with $R = 0.03$ $\mu A/(cm^2 \cdot s)$. Membrane starts from resting state at $t = 0$ with $I_0 = 0$. (*B*) Time course of extracellular (γ) cAMP for slowly tuned, three-variable, model (Eqs. 3 of [4]) of signaling system that controls aggregation of slime mold *Dictyostelium discoideum* after starvation. Four parameters, identified as affecting developmental transitions from steady to oscillatory behavior (6), are ramped from zero at different speeds: $\sigma = 2.2 \times 10^{-3} t$, $k_e = 9.3 \times 10^{-2} t$, $k_i = 3 \times 10^{-3} t$), $F_R = 2.6 \times 10^{-3} t$; σ, k_e, k_i have units min^{-1} and F_R is dimensionless. Initial conditions: $\rho_T(0) = 0$, $\beta(0) = 0$, $\gamma(0) = 0.127$.

activity for a steady stimulus arises as a damped oscillation changes into a maintained oscillation.[1] While some aspects of the HH theory are considered in need of revision (e.g., [10]), the specific form of the model is not crucial to our conclusions. The above qualitative feature should be shared by any alternative model which seeks to account for the oscillatory properties seen in squid (11, 12), or similar properties in other systems. For these reasons, and in order to relate directly to the motivating study of Jakobsson and Guttman, we use the HH case to illustrate our results.

The HH model exhibits repetitive firing in response to a steady current if the current strength is in an appropriate range $I_1 < I < I_2$ (13, 14); the values $I_{1,2}$ are computed by a linearized theory. This suggests that if the current is applied as a slow ramp then the repetitive response should be elicited as the current passes a critical level. Jakobsson and Guttman (7, 8) demonstrated this for the HH model, and for squid axon, and they emphasized that neither exhibits full accommodation no matter how slow the ramp. They found, for a ramped current in the model, that the observed or apparent threshold level, I_j, typically exceeds the steady threshold value I_1. Furthermore, as we show here, the deviation $I_j - I_1$ depends on the initial current I_0, so that there is a memory effect associated with the slow tuning. The calculations of Jakobsson and Guttman also showed that I_j depends on the ramp speed, R, and in a surprising nonmonotonic way. For moderately slow ramps, I_j increases as the ramp speed decreases; one might say that the HH membrane shows partial accommodation. For much slower ramp speeds however, the computed I_j shows a decreasing trend as R decreases; it was suggested that the HH model, and squid axon in low calcium, exhibit reverse accommodation.

Our work indicates that the reverse accommodation feature of the nonmonotonic behavior is characteristic of a class of systems when a stimulus, or parameter, is slowly tuned through a threshold value. It reflects the influence of persistent random fluctuations, i.e., for very slow tuning, there is a longer time for fluctuations to accumulate and to increase the chance of firing, thereby resulting in a lower value of I_j. We have also derived analytically a condition which yields an approximation for I_j in the idealized case of a slow ramp when fluctuations are ignored. This condition, based on our deterministic analysis, predicts that I_j should exceed the critical value, I_1 (the steady current at which the depolarized rest potential loses stability), and moreover, that the deviation depends on I_0. Thus, one observes a memory effect when the current is ramped slowly from a stable holding state. However this effect is diminished in the presence of significant environmental fluctuations.

Numerical computations were performed on a Vax 11/8600 and the IBM System 3090 Vector Facility. We used a classical fourth-order Runge-Kutta method with fixed time step of 0.05. The computer program was written to use vector instructions to advantage. Vectorization over parameter space (e.g., ramp speed) results in a significant decrease in execution time.

Fig. 2 illustrates the dependence of I_j upon $1/R$; slower ramp speed is in the rightward direction, and each point is for a different value of R. At $t = 0$, the membrane is at rest and $I_0 = 0$. Notice first, the delay effect, i.e., the deviation $I_j - I_1$. For all but the fastest ramps, the slowly rising current must pass above I_1, the threshold for repetitive firing for a steady current, before an action potential

[1] In mathematical terms this type of transition from steady state to periodic behavior is called a Hopf bifurcation (9). It is one of the few generic ways in which periodic solutions arise. Both hard oscillations and soft oscillations may originate as Hopf bifurcations. (i.e., sub- and supercritical bifurcations, respectively [9]); The HH model exhibits each type at I_1 and I_2, respectively (14).

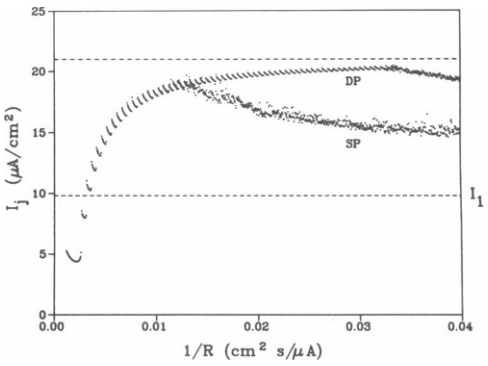

FIGURE 2 The onset of repetitive firing depends on ramp speed R as well as on persistent fluctuations; from numercial integration of the standard HH equations at 6.3°C. Each plotted point denotes the current I_j at which the first action potential occurs (when the membrane potential first exceeds 40 mV above rest). For each ramp, the membrane is initiated from rest and the current starts at zero. The lower dashed line is the threshold values for a steady current, $I_1 = 9.78$ μA/cm^2, and the upper dashed line is an analytical prediction of I_j for a very slow ramp in a noise-free system. Results for two levels of precision, single (SP) and double (DP), are superimposed to show the effects of fluctuations due to roundoff error. The data points SP depart from the DP results near $1/R = 0.01$. For double precision, flucutations have an effect only at much slower ramp speeds ($1/R > 0.03$).

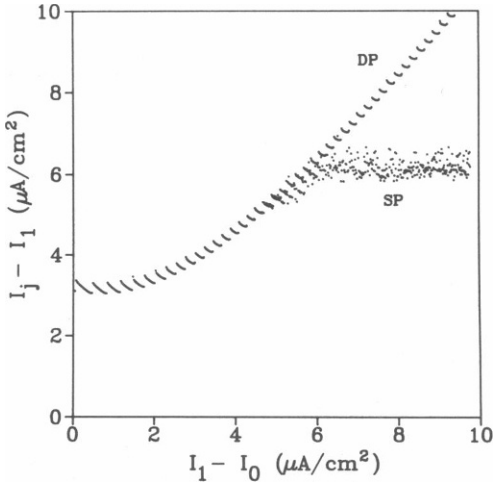

FIGURE 3 The memory effect. When current is initiated from rest, the onset of firing is delayed until I sufficiently exceeds the steady threshold $I_1 = 9.78$ μA/cm^2. Each point is for a different initial current I_0; ramp speed $R \simeq 33.3$ μA·cm^2/s. Computations in single precision (SP) show that fluctations due to roundoff error can destroy the memory effect for $I_1 - I_0 > 5$, whereas in double precision (DP) the memory effect remains over the range shown. Temperature is 6.3°C.

occurs. Our analytic results predict, if the ramp is very slow and if the environment is noise-free, that I_j is about as far above I_1 as the initial current ($I_0 = 0$ for Fig. 2) is below I_1; the upper dashed horizontal line illustrates this prediction for the HH model.

Next we focus on the data labeled SP, and we identify two behaviors: a net increasing trend on the left and a decreasing trend on the right. The increasing trend is consistent with the notion of accommodation (1, 15, 16); a slower stimulus leads to an effectively increased threshold. These data on the left also exhibit a fine structure: localized regions of decreasing I_j but with abrupt increases to create a sawtooth appearance. The sawtooth feature, as also interpreted by Jakobsson and Guttman, reflects the susceptibility of the membrane to fire during the depolarizing phase of a subthreshold oscillation. Each short decreasing segment of a sawtooth corresponds to firing approximately after a certain number n of subthreshold oscillations; these segments are pieces of hyperbolae: $(1/R)I_j = n \cdot T_s$, where T_s equals the period of the subthreshold oscillations. The nearly discontinuous jumps in I_j correspond to adding one more subthreshold oscillation ($n \rightarrow n + 1$) so that these jumps approximately equal $R \cdot T_s$, and therefore they become smaller for smaller R.

The data on the right in Fig. 2, the decreasing portion, have an identifiably different structure. The regular sawtooths are absent and the data appear to reflect some stochasticity. This different structure was not noticeable in the results of Jakobsson and Guttman because they had so few data points for small R. Since the HH model is deterministic and the numerical integration algorithm is deterministic we were led to consider machine roundoff error as the likely source of randomness; please note that roundoff error is distinct from the truncation error of a finite difference method. In order to demonstrate the effect of roundoff, the calculations were repeated in double precision, and plotted here with the label DP. The sawtooth data were reproduced and the increasing trend was extended to slower ramp speeds before the much smaller roundoff errors could interfere with the memory effect. We conclude that this decreasing trend does not reflect a special biophysical mechanism, reverse accommodation, which is unique to the HH model. Other systems (17, 18) which exhibit a memory effect have also shown similar sensitivity to random fluctuations. Furthermore, we have found in double or quadruple precision calculations of slow passage through threshold for the HH model, and for a canonical model of excitability (17), that small amplitude, additive white noise mimics the influence of single precision round-off error. We remark that this magnitude of noise is comparable with that of conductance fluctuations in a 1-cm^2 patch of HH membrane. With a simplified model (HH with white noise Na^+- and K^+-conductance fluctuations on the order of $1/\sqrt{N}$, where $N = 10^9$ channels) we have generated results which resemble those in Fig. 2.

For the above calculations, the membrane and applied current were initiated from rest, and we observed a time delay in the onset of firing until I sufficiently exceeded I_1.

[2]This condition is derived under the assumption that the slowest decaying mode (for $I < I_1$) of the linearized equations is oscillatory. The assumption is valid for the HH equations over a substantial range of I but violated slightly for I_0 near zero, nevertheless the integral condition yields a good approximation of the computed results for I_j.

The results of Fig. 3 show, for a given ramp speed, how $I_j - I_1$ depends on the deviation, $I_1 - I_0$, of the initial current from the steady-current threshold. This dependence emphasizes the memory aspect: over a certain range of initial states, the greater is $I_1 - I_0$ then the greater is $I_j - I_1$. These numerical results are in agreement with our analytic results which are asymptotic for a very slow ramp in a noise-free system (17). This analysis shows that I_j satisfies the following condition:[2]

$$0 = \int_{I_0}^{I_j} Re\,\{\lambda(I)\}\,dI, \tag{1}$$

where, $Re\,\{\lambda(I)\}$ is the exponential decay rate of subthreshold oscillations, (which is negative) when I is below I_1, and the growth rate (positive) of small oscillations when I is above I_1. For $I = I_1$, $Re\{\lambda(I)\}$ passes through zero, $Im\{\lambda(I)\}$ is nonzero, and this characterizes the (Hopf bifurcation [9]) threshold I_1 for steady current at which the depolarized state changes stability from an attracting spiral to a repelling spiral. Because this is an integral condition we see immediately that I_j must exceed I_1; the accumulating effect of exponential decay for $I < I_1$ must be balanced by sufficient influence of a growing mode.

The derivation of this integral condition (Eq. 1) is motivated by an observation that when the current is slowly ramped from rest, the system closely tracks the steady-state solution of the static problem. Therefore, a slowly-varying solution can be derived as a perturbation from the steady-state solution. To check stability, we linearize the full problem about the slowly-varying solution and determine when the linear system exhibits exponential growth. To solve the linear problem we use a classical asymptotic method of mathematical physics, the (Wentzel-Kramers-Brillouin) method (19), and seek an asymptotic expansion, for each dependent variable, of the form

$$y(\tau) \sim \exp\left[\frac{\sigma(\tau)}{R}\right][y_0(\tau) + Ry_1(\tau) + R^2y_2(\tau) + \cdots], \tag{2}$$

where

$$R \ll 1,\ \tau = Rt \text{ and } \sigma(\tau) = \sigma_0(\tau) + R\sigma_1(\tau) + R^2\sigma_2(\tau) + \cdots.$$

Here, R is the ramp speed, τ is the slow time variable, and y_i, σ_i are to be determined. The WKB formulation seeks the solution as a rapidly-varying phase function, with a slowly modulated amplitude (the $y_i(\tau)$ series). Exponential growth occurs when $Re\{\sigma(\tau)\}/R$ is of order 1; in the limit as R tends to zero, this means $Re\{\sigma(\tau)\} = 0$. When this expansion in Eq. 2 is substituted into the linear system, a solvability condition is found for y_0 that requires

$$\frac{d}{d\tau}\,[Re\,\{\sigma_0(\tau)\}] = Re\,\{\lambda(I(\tau))\}, \tag{3}$$

where $Re\,\{\lambda(I(\tau))\}$ is defined is the preceding paragraph. The stability criterion (Eq. 1) follows by integrating Eq. 3 with respect to τ, setting $Re\,\{\sigma_0\}$ equal to zero and changing the integration parameter from τ to I.

For the special case when I_0 is very close to I_1, the integral condition implies that I_j must also be very close to (just barely above) I_1. The data of Fig. 3 deviate from this prediction; for $I_0 = I_1$, $I_j - I_1$ is ~3. This discrepancy arises because the integral condition is derived asymptotically as R tends to zero.

For small, but nonzero R, and for I_0 near I_1, the growth condition for Eq. 2 means that the integral condition is written in the more precise form

$$kR = \int_{I_0}^{I_j} Re\,\{\lambda(I)\}\,dI, \tag{4}$$

where k is an order one constant. Furthermore, by using a Taylor's series approximation for $Re\,\lambda$ when $I - I_1$ is small, i.e., $Re\,\lambda \simeq \bar{\lambda}\,(I - I_1)$, where $\bar{\lambda}$ is an appropriate positive constant (for HH, $\bar{\lambda} \simeq 0.02$), we obtain the improved estimate

$$I_j - I_1 = [(2\,kR/\bar{\lambda}) + (I_1 - I_0)^2]^{1/2}. \tag{5}$$

Thus, if kR is comparable in magnitude to $\bar{\lambda}$, then the memory aspect is still present but not dominant. This formula predicts the zero slope for I_0 near I_1 in Fig. 3, and with $k = 2.7$ we compute $I_j - I_1 \simeq 3$ for $I_0 = I_1$.

The results of Fig. 3 further show that if the initial current is sufficiently below I_1 then there is enough time, as the current increases, for fluctuations to take effect and to decrease the memory effect. In this situation the membrane no longer distinguishes initial states which are too far away; the data in Fig. 3 that are labeled SP (from single-precision calculations) thus level off for $I_1 - I_0$ greater than a certain value. With double precision arithmetic (data labeled DP), the HH membrane, responding to a slow current ramp, is capable of recognizing different initial states which are more distant.

Parameter changes that affect membrane dynamics and the steady thresholds I_1 and I_2 will also alter the memory effect. For example, at higher temperature I_1 is larger and I_2 is smaller. If the difference $I_2 - I_1$ is not too large then one can expect that the membrane in response to a slow ramp (from a holding state not too far from I_1) would not exhibit repetitive firing; the current would sweep right through the vulnerable range without eliciting an action potential. Stimulus configuration and geometry also have an effect. Here, we have considered a space-clamped membrane. For an HH cable model subjected to a spatially localized ramping stimulus one may find an apparent accommodation; cable properties induce an additional load that will result in a different range, $I_2 - I_1$, which may be smaller (20, 21). In these considerations however, one must be aware from our results, that the influence of fluctuations can be significant. For interpreting steady-state threshold criteria, and for comparing with experimental behaviors, one must consider the dynamic effect of slowly tuning a stimulus in the presence of persistent

fluctuations. These joint considerations may be adequate to explain various aspects of accommodative phenomena, on certain time scales at least, without having to hypothesize additional biophysical mechanisms. Finally, we emphasize again that our results apply generally to systems which exhibit similar threshold-crossing behavior to the HH model (e.g., [1–5]), i.e., the local behavior around steady state is decaying oscillations and changes to growing oscillations as the steady-stimulus parameter is increased beyond threshold. Such models exhibit a finite minimum firing frequency. Another class of excitable membrane model is characterized by a zero firing frequency at threshold, e.g., the model formulated by Rall (22) and simplified versions of Conner's model (23). Our preliminary numerical experiments with such models do not reveal a noticeable memory effect.

We thank both Dr. Jacob Maizel at the Frederick Cancer Research Facility Supercomputer Center and the Division of Computer Research and Technology at National Institutes of Health for providing computer time. We also thank Dr. Arthur S. Sherman for helpful comments and suggestions.

REFERENCES

1. Hodgkin, A. L., and A. F. Huxley. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.).* 117:500–544.
2. Morris, C., and H. Lecar. 1981. Voltage oscillations in the barnacle giant muscle fiber. *Biophys. J.* 35:193–213.
3. Chay, T. R., and Y. S. Lee. 1985. Phase resetting and bifurcation in the ventricular myocardium. *Biophys. J.* 47:641–651.
4. Martiel, J. L., and A. Goldbeter. 1987. A model based on receptor desensitization for cyclic AMP signaling in Dictyostelium cells. *Biophys. J.* 52:807–828.
5. Hervahault, J. F., M. C. Duban, J. P. Kernevez, and D. Thomas. 1983. Multiple steady states and oscillatory behavior of a compartmentalized phosphofructokinase system. *Proc. Natl. Acad. Sci. USA.* 52:5455–5459.
6. Goldbeter, A., and J. L. Martiel. 1987. Developmental control of a biological rhythm: the onset of cyclic AMP oscillations in Dictyostelium cells. *In* From Chemical to Biological Organization. M. Markus, S. Muller, and G. Nicolis, editors. Springer-Verlag GmbH & Co. KG, Heidelberg, Berlin.
7. Jakobsson, E., and R. Guttman. 1980. The standard Hodgkin-Huxley model and squid axons in reduced Ca^{++} fail to accommodate to slowly rising currents. *Biophys. J.* 31:293–298.
8. Jakobsson, E., and R. Guttman. 1981. Continuous stimulation and threshold of axons: the other legacy of Kenneth Cole. *In* Biophysical Approach to Excitable Systems. W. Adelman and D. Goldman, eds. Plenum Publishing Corp., New York 197–211.
9. Hassard, B. D., N. D. Kazarinoff, and Y-H Wan. 1981. Theory and applications of Hopf bifurcation. Cambridge University Press. Cambridge, MA.
10. Aldrich, R. W., D. P. Corey, and C. F. Stevens. 1983. A reinterpretation of mammalian sodium channel gating based on single channel recording. *Nature (Lond.).* 306:436–441.
11. Guttman, R., and R. Barnhill. 1970. Oscillation and repetitive firing in squid axons. Comparison of experiments with computations. *J. Gen. Physiol.* 55:104–118.
12. Mauro, A., F. Conti, F. Dodge, and R. Schor. 1970. Subthreshold behavior and phenomenological impedance of the squid giant axon. *J. Gen. Physiol.* 55:497–523.
13. Cooley, J., F. Dodge, and H. Cohen. 1965. Digital computer solutions for excitable membrane models. *J. Cell. Comp. Physiol.* 66 (Supp. 2):99–109.
14. Rinzel, J. 1978. On repetitive activity in nerve. *Fed. Proc.* 37:2793–2802.
15. Vallbo, A. B. 1964*a*. Accommodation of single myelinated nerve fibres from *Xenopus laevis* related to type of end organ. *Acta. Physiol. Scan.* 61:413–428.
16. Vallbo, A. B. 1964b. Accommodation related to inactivation of the sodium permeability in single myelinated nerve fibres from Xenopus. *Acta. Physiol. Scand.* 61:429–444.
17. Baer, S. M., T. Erneux and J. Rinzel. 1987. The slow passage through a Hopf bifurcation: delay, memory effects and resonance. *SIAM J. Appl. Math.* In press.
18. Fronzoni, L., F. Moss and P. V. E. McClintock. 1987. Swept parameter induced postponements and noise on the Hopf bifurcation. *Phys. Rev.* A 36:1492–1494.
19. Bender, C. M., and S. A. Orzag. 1978. Advanced mathematical methods for scientists and engineers. McGraw-Hill Book Co., New York, 484–543.
20. Baer, S. M., and C. Tier. 1986. An analysis of a dendritic neuron model with an active membrane site. *J. Math. Biol.* 23:137–161.
21. Rinzel, J., and J. P. Keener. 1983. Hopf bifurcation to repetitive activity in nerve. *SIAM J. Appl. Math.* 43:907–922.
22. Rall, W., and G. M. Shepherd. 1968.Theoretical reconstruction and dendrodendritic synaptic interactions in olfactory bulb. *J. Neurophysiol. (Bethesda).* 31:884–915.
23. Connor, J. A., D. Walter, and R. McKown. 1977. Neural repetitive firing: modifications of the Hodgkin-Huxley axon suggested by experimental results from crustacean axons. *Biophys. J.* 18:81–102.